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EXAMINER	
RAWLINGS, STEPHEN L	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/512,581	Applicant(s) SOTO ET AL.	
	Examiner Stephen L. Rawlings, Ph.D.	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-67* is/are pending in the application.

4a) Of the above claim(s) *3,13-46,50 and 52-67* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-12,47-49 and 51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-67* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply* .

DETAILED ACTION

1. The election without traverse of Group I, claims 1, 2, 4-12, 47-49, and 51, filed on September 10, 2001 in Paper No. 9 is acknowledged and has been entered.

2. Claims 1-67 are pending in the application. As stated in Paper No. 6, claim 3 has been withdrawn from further consideration as being drawn to undisclosed subject matter. Claims 13-46, 50, and 52-67 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

3. Claims 1, 2, 4-12, 47-49, and 51 are currently under prosecution.

Compliance to Sequence Rules

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

In particular, it is noted that the amino acid sequence disclosed on page 78 of the specification is of sufficient length to require compliance to the Sequence Rules. In addition, Applicant is directed to refer to the grounds of rejection under 35 USC § 112, first paragraph rejection, which are set forth below. Applicant is required to correct any errors or discrepancies in the Sequence Listing or the disclosure, but cautioned against the introduction of new matter into the specification by any amendment to correct such errors or discrepancies.

Applicant is given the same period of time within which to comply with the Sequence Rules under 37 C.F.R. §§ 1.821-1.825 as within which to reply to this

Office Action. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. § 1.821(g). Applicant is requested to return a copy of the attached Notice to Comply with the response.

Claim Objections

5. Claims 3, 6-12, and 51 are objected to because of the following informalities:

As stated in the previous Office Action, claim 3 is incomplete because of the omission of the ATCC accession number. The claim will not be further examined because the subject matter of the claim cannot be determined.

Claims 6-12 are objected to because the claims depend from claim 3 and therefore are also drawn in the alternative to non-disclosed subject matter.

Claim 51 is objected to because the claim is drawn to the subject matter of a non-elected invention.

Appropriate corrections are required.

Specification

6. The disclosure is objected to because of the following informalities: Throughout the specification, the ATCC accession number(s) have been omitted.

Appropriate correction is required.

7. The disclosure is objected to because the disclosure refers to embedded hyperlinks and/or other forms of browser-executable code, which are impermissible and require deletion.

The attempt to incorporate subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP § 608.01(p), paragraph I regarding incorporation by reference.

8. The use of the numerous trademarks has been noted in this application. Each letter of a trademark should be capitalized or otherwise the trademark

should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ©, ®), and accompanied by generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Claim Rejections - 35 USC § 101

9. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

10. Claims 47 and 51 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible asserted utility or a well-established utility.

Claim 47 is drawn to a kit for use in diagnosing a mammal with an increased likelihood for developing a disease having pathology involving abnormal cellular proliferation. Because according to the claim, the kit comprises a material for use in measuring an amount of messenger RNA (mRNA) encoding AS3, it is reasonably apparent that Applicants intend the invention to be used to measure the amount of mRNA encoding AS3 and to somehow determine the mammal's likelihood of developing a proliferative cell disorder, such as cancer, by consideration of the measured amount of mRNA encoding AS3.

Claim 51 is drawn to a kit for use in determining whether a subject is at increased risk for developing prostate cancer. According to the claim, the kit will comprise a set of instructions for determining whether the subject is at increased risk for developing prostate cancer by first detecting the presence or absence of AS3 in the subject and then observing whether or not the subject is at increased risk for developing prostate cancer. Furthermore, according to the claim, a subject is at increased risk for developing prostate cancer if the absence of or reduced levels of AS3 are detected.

With regard to claim 47, the invention does not have a well-established utility and the asserted utility lacks credibility since the specification does not actually teach how the invention can be used to determine the likelihood that a mammal will develop a proliferative cell disorder by measuring the amount of mRNA encoding AS3. The specification does not provide working exemplification of the use of the invention to determine the likelihood that a mammal will develop a proliferative cell disorder and moreover there is clearly insufficient guidance disclosed therein to enable one of skill in the art to use the invention to do so. In fact, it is not even clear when and where the kit should be used to measure the amount of mRNA encoding AS3 or in which cells of the mammal the measurement should be made, but more critically the specification fails to demonstrate the relationship between the amount of mRNA encoding AD3 and the likelihood that a mammal will develop a proliferative cell disorder. Certainly, in the absence of essential guidance and working exemplification, because of the high level of unpredictability in the art, one of skill in the art would not accept the assertion that the invention can be used to successfully predict whether a mammal will develop a proliferative cell disorder based only upon a determination of the amount of mRNA encoding AS3. Accordingly, the invention is not supported by a credible asserted utility.

With regard to claim 51, the invention does not have a well-established utility and in the absence of working exemplification of the use of the invention to effectively and accurately determine if a subject is at increased risk for developing prostate cancer due to a lack of or a reduction in the level of expression of the gene encoding AS3, the invention lacks a credible asserted utility. Based only upon the disclosure, one skilled in the art would not accept the assertion that the invention can be used to successfully determine whether or not a subject is at increased risk for developing prostate cancer. In particular, it is noted that the specification does not demonstrate that a statistically significant correlation exists between a lack of or a reduction in the expression of the gene encoding AS3 in a subject and the frequency of incidence of prostate cancer in multiple and different subjects. In the absence of a disclosure demonstrating that

such a correlation exists, the skilled artisan would not find the asserted utility credible. For example, according to the claim, Applicants propose that the invention can be used to determine whether or not a subject is at increased risk for developing prostate cancer by the process of first determining if the subject has an absence of or a reduced level of AS3 and then waiting until the subject either does or does not develop prostate cancer. Presumably, if the subject develops prostate cancer, and it was determined at some time in the past that the subject had an aberrant level of AS3, then one would conclude the subject was in fact at increased risk for developing prostate cancer due to the abnormal expression of the gene encoding AS3. To the contrary, however, without supportive data, one skilled in the art would not conclude that the absence of or the reduction in the expression of AS3 was causative of the disease or had placed the subject at increased risk for having had developed the disease, because such an assumption would be highly unreasonable.

Finally, with regard to claimed subject matter of both claims 47 and 51, it well appreciated by one of ordinary skill in the art that the etiology of cancer is a highly complex process and most will agree, the development of cancer cannot be linked to a single epigenetic event, such as a mutation in the coding sequence of a tumor suppressor; therefore, it is improbable that the lack of or a reduction in the level of expression of the gene encoding AS3 will prove to be significantly associated with an increased likelihood or risk for developing prostate cancer. Therefore, to establish a credible utility for the invention, one would necessarily need to conduct a carefully controlled, multi-center epidemiological study and to judiciously evaluate the results of the study by statistical analysis. Furthermore, testing for predisposition to cancer should be offered only after the test has been validated and the results can be adequately interpreted and only when the results will influence the medical disease management for the subject or the subject's relations.

For the reason set forth in the paragraphs above, it is not evident that the invention is supported by a credible asserted utility and therefore the claims fail

to meet the requirements of 35 USC § 101. Additional support for this position is set forth in the 35 USC § 112, first paragraph rejections below.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 47 and 51 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The claims are drawn to a kit for use in a method for determining a subject's risk for developing prostate cancer or some other undisclosed proliferative cell disorder, which according to the specification can be used to prevent or delay the incidence or onset of the disease or disorder. As stated in the 35 USC § 101 rejection above, the mere premise upon which the usefulness of the invention relies is not supported by either sufficient or conclusive data, therefore precluding the usefulness of risk assessment in cancer prevention, in general. One skilled in the art cannot predict the effectiveness and accuracy of the claimed method for determining a subject's risk for developing cancer. Moreover, one skilled in the art cannot predict whether knowledge of a single risk factor, which in this case is determined by measuring the cytotoxicity of a subject's diagnostic cells, will be instrumental in preventing prostate cancer or other proliferative cell disorder. This lack of predictability is due to the absence of a showing that there is a scientifically and clinically significant correlation between this risk factor and the occurrence or recurrence of the disease or disorder in a subject. Furthermore, because there are other risk factors associated with an individual's risk for developing a proliferative cell disorder, which may contribute even more significantly than the proposed risk factor, it is doubtful that the method can effectively and accurately be used to predict

whether the disease or disorder will develop in a subject. In the absence of sufficient exemplification and guidance in the specification that teach how the claimed invention can be used to make such predictions, one skilled in the art is not reasonably apprised of how to use the invention. Furthermore, the claims are drawn to a method of determining a subject's risk for developing *any* type of proliferative cell disorder, including *any* type of prostate cancer; yet, certainly the assessment of risk by the claimed method will not be shown to be equally predictive of a subject's tendency to develop any and all types of proliferative cell disorders or tumors without regard to either etiology or the tissue of origin. For these reasons, clearly one skilled in the art would not know how to use the claimed invention to identify individuals at risk for developing cancer with a reasonable expectation of success without undue experimentation.

13. Claims 1, 2, 4-12, 47-49, and 51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to nucleic acid molecules, vectors and host cells that comprises said nucleic acid molecules, and methods that depend upon the use of said nucleic acid molecules.

The teachings of the specification cannot be extrapolated to the enablement of the invention commensurate in scope with the claims because there are a number of discrepancies between the polynucleotide sequences disclosed in the specification and the corresponding polynucleotide sequences reported in the literature or submitted to publicly accessible databases.

In particular, it is noted that Geck, et al submitted a polynucleotide sequence having the accession number U95825 to Database GenEMBL, which according to the sequence annotation is the complete coding sequence of a messenger RNA (mRNA) molecule isolated from human LNCaP prostate cancer cells and which is designated human androgen-induced prostate proliferative shutoff associated protein (AS3). Also, it is noted that Geck, et al published the

polynucleotide sequence of the full length cDNA encoding AS3 in the Jaunary 1999 issue of the *Journal of Steroid Biochemistry and Molecular Biology* (Vol. 68, No. 1-2, pp. 41-50; see Figure 1), wherein Geck, et al disclose that the nucleotide sequence reported in the paper had been submitted to GenBank with accession number U95825. With regard to the instant application, the specification teaches that the polynucleotide sequence of the full-length cDNA encoding AS3 is set forth in SEQ ID NO: 1. However, the polynucleotide sequences of SEQ ID NO: 1 and GenEMBL Accession No. U95825 are not identical, as one would expect. In fact, after an optimal alignment, there is only an 80.3% correspondence between the two sequences, which are mismatched at 20 different positions throughout the sequences.

While the specification apparently offers no disclosure that might explain these discrepancies or serve to instruct the practitioner that the polynucleotide sequences reported elsewhere are considered to be accurate, it is further noted that there are discrepancies between the polynucleotide sequences of the disclosure, including the figures, and polynucleotide sequences of the sequence listing. Again, the specification discloses that the polynucleotide sequence of SEQ ID NO: 1 is the polynucleotide sequence of the cDNA molecule encoding human AS3, which is also shown in Figure 1 (page 13, lines 30-32). According to the sequence listing, SEQ ID NO: 1 consists of 5,271 nucleotides. However, according to the *Brief Description of the Drawings* on page 9 of the specification, while Figure 1 supposedly also depicts the polynucleotide sequence of the cDNA encoding AS3, the sequence of Figure 1 consists of only 5,253 nucleotides. The reason that the sequence of Figure 1 and the sequence of SEQ ID NO: 1 are different is not immediately apparent.

Perhaps of greater concern, however, is the observation that the amino acid sequence encoded by the polynucleotide sequence of SEQ ID NO: 3, which the specification teaches is the open reading frame, i.e., coding sequence, of the cDNA molecule, encodes a protein that has an amino acid sequence that differs from the amino acid sequence of SEQ ID NO: 2, which the specification discloses as being the amino acid sequence encoded by SEQ ID NO: 3.

Obviously, since the translated amino acid sequence differs from the amino acid sequence of AS3 (i.e., SEQ ID NO: 2), there is an error in either SEQ ID NO: 3 or SEQ ID NO: 2 and likely also, an error in the amino acid sequences of the figures.

In light of these discrepancies and/or errors, there is a reasonable doubt that the disclosure of the invention meets the enablement requirement of 35 USC § 112, first paragraph. Any inaccuracies in the polynucleotide or polypeptide sequences disclosed in the specification would preclude the successful practice (i.e., production and/or use) of the invention. For this reason, one skilled in the art would not be able to practice the invention commensurate in scope with the claims with a reasonable expectation of success without first performing undue experimentation.

Amendment of the claims and specification to resolve the discrepancies will likely be required; however, Applicant is cautioned against the introduction of new matter if amendments and/or corrections are made to the specification, including the claims, the figures, and the sequence listing.

14. If Applicant were able to overcome the 35 USC § 112, first paragraph rejection above, claims 4-12 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid molecule comprising the polynucleotide sequence set forth in SEQ ID NO: 1 or 3 or the complement thereof, a vector comprising said nucleic acid molecule, a host cell comprising said vector, and a method for producing the polypeptide encoded by said nucleic acid molecule, does not reasonably provide enablement for an isolated nucleic acid molecule encoding a naturally occurring allelic variant of the polypeptide of SEQ ID NO: 2, encoding any polypeptide comprising an amino acid sequence at least about 45% homologous to the amino acid sequence of SEQ ID NO: 2, or encoding any fragment of a polypeptide comprising at least 15 contiguous amino acid residues of the amino acid sequence of SEQ ID NO: 2, does not reasonably provide enablement for any isolated nucleic acid molecule comprising a nucleotide sequence that is at least

50% homologous to the nucleotide sequence of SEQ ID NO: 1 or 3 or the complement thereof or comprising a fragment of at least 250 nucleotides of a nucleic acid comprising the nucleotide sequence of SEQ ID NO: 1 or 3 or the complement thereof, does not reasonably provide enablement for an isolated nucleic acid molecule that hybridizes under stringent conditions to the nucleic acid of any one of claims 1, 2, 3, 4, or 5, does not reasonably provide enablement for an isolated nucleic acid molecule comprising the complement of any of the foregoing isolated nucleic acid molecules, does not reasonably provide enablement for a vector comprising any of the foregoing isolated nucleic acid molecules, and does not reasonably provide enablement for a method for producing the polypeptide encoded by any of the foregoing isolated nucleic acid molecules. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 4-12 are drawn to nucleic acid molecules, vectors comprising those nucleic acid molecules, host cells comprising those vectors, and a method for producing a polypeptide, which comprises culturing those host cells.

The teachings of the specification cannot be extrapolated to the enablement of the claimed invention because there is insufficient guidance and exemplification disclosed therein, which is commensurate in scope with the claims, to enable one skilled in the art to make and to use the claimed invention. To meet the enablement requirement of 35 USC § 112, first paragraph, the specification must provide a level of guidance for and exemplification of the practice of the claimed invention, which is reasonably commensurate in scope with the claims. However, it is clear that the disclosure does not teach one to make and/or use all of the embodiments of the invention that are encompassed by the claims and furthermore, in the absence of such essential disclosure, one skilled in the art would not be able to make and/or use the invention with a reasonable expectation of success without first performing undue experimentation.

In particular, the specification does not reasonably provide enablement for a method for producing the polypeptide encoded by any of the isolated nucleic acid molecules that are encompassed by the claims. For example, it is noted that the protein having the amino acid sequence set forth as GenBank Accession No. AB014548 is encompassed by claim 5, because the protein is encoded by an isolated nucleic acid molecule that encodes at least 15 contiguous amino acid residues of SEQ ID NO: 2. However, the specification most certainly does not teach a method for either making or using this protein, but moreover one skilled in the art would not expect to be able to use this protein in accordance with the teachings of the specification, because it is highly improbable that this protein will have the same or even similar structure and function that AS3 has. Therefore, the specification does not reasonably provide enablement for an isolated nucleic acid molecule encoding any fragment of a polypeptide comprising at least 15 contiguous amino acid residues of the amino acid sequence of SEQ ID NO: 2 or for that matter, a vector or host cell comprising the nucleic acid molecule.

For the same reason, the specification does not reasonably provide enablement for any isolated nucleic acid molecule comprising a fragment of at least 250 nucleotides of a nucleic acid comprising the nucleotide sequence of SEQ ID NO: 1 or 3 or the complement thereof or a vector or host cell comprising such a nucleic acid molecule. For example, the isolated nucleic acid molecule of GenBank Accession Number AC068224 consists of a nucleic acid molecule comprising a fragment of at least 250 nucleotides of a nucleic acid comprising the nucleotide sequence of SEQ ID NO: 1 or 3, but where in the specification is a method for producing and using the nucleic acid disclosed? Again, one skilled in the art would not expect to be able to use this nucleic acid or the protein which it encodes in accordance with the teachings of the specification, because it is highly improbable that the protein will have the same or even similar structure and function that AS3 has.

Similarly, the specification does not reasonably provide enablement for an isolated nucleic acid molecule encoding a naturally occurring allelic variant of the polypeptide of SEQ ID NO: 2 or encoding any polypeptide comprising an amino

acid sequence at least about 45% homologous to the amino acid sequence of SEQ ID NO: 2 and does not reasonably provide enablement for any isolated nucleic acid molecule comprising a nucleotide sequence that is at least 50% homologous to the nucleotide sequence of SEQ ID NO: 1 or 3 or which reasonably provide enablement for an isolated nucleic acid molecule that hybridizes under stringent conditions to the nucleic acid of any one of claims 1, 2, 3, 4, or 5.

Bowie, et al (*Science* **257**: 1306-1310, 1990) teach that an amino acid sequence encodes a message that determines the shape and function of a protein; and, that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome. The cited reference also teaches that the prediction of protein structure from sequence data and, in turn, utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (page 1306, column 1). Bowie, et al teach that while it is known that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship and these regions can tolerate only conservative substitutions or none at all (page 1306, column 2).

Burgess, et al (*Journal of Cell Biology* **111**: 2129-2138, 1990) exemplifies the sensitivity of proteins to alterations of even a single amino acid in a sequence. This reference teaches that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. As another example of the unpredictability in the art, Lazar et al (*Molecular and Cellular Biology*, 1988, **8**: 1247-1252) teach that a replacement of aspartic acid at position 47 with alanine or asparagine in transforming growth factor alpha had no effect but that a replacement with serine or glutamic acid sharply reduced its biological activity.

Considering the teachings of the references cited above, it is apparent that even a single conservative amino acid substitution often dramatically affects the biologic activity and the structure-function characteristics of a protein. Therefore, it is clear that one skilled in the art cannot immediately envision the proteins encoded by the claimed nucleic acid molecules and moreover could not predict whether an allelic variant of the polypeptide of SEQ ID NO: 2 or any other polypeptide comprising an amino acid sequence at least about 45% homologous to the amino acid sequence of SEQ ID NO: 2, which might be encoded by the claimed nucleic acid molecule comprising a nucleotide sequence that is at least 50% homologous to the nucleotide sequence of SEQ ID NO: 1 or 3 or which hybridizes under stringent conditions to the nucleic acid of any one of claims 1, 2, 3, 4, or 5, can be used in the same or similar manner as the protein of SEQ ID NO: 2. Hence, because the specification does not exemplify the use of the broad genus of nucleic acid molecules or the proteins encoded thereby that is encompassed by the claims, one skilled in the art would not be able to make and/or the nucleic acid molecules or the proteins with a reasonable expectation of success in accordance with the teachings of the specification without first performing undue experimentation.

For the reason set forth above, the disclosure fails to meet the enablement requirement of 35 USC § 112, first paragraph.

15. If Applicant were able to overcome the 35 USC §§ 101 and 112, first paragraph rejections above, claims 47 and 51 would still be rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As stated to some extent in the 35 USC § 101 rejection above, claim 47 is drawn to a kit for use in diagnosing a mammal with a disease with pathology involving altered cellular proliferation or for use in determining whether a mammal has an increased likelihood for developing such a disease, wherein said

kit comprises a means for measuring the amount of mRNA encoding AS3 in a sample. Claim 51 is also drawn to a kit for use in determining whether a subject is at increased risk for developing a proliferative cell disorder, although the claim specifically names prostate cancer as the disorder. According to claim 51, the kit comprises antibodies that selectively bind to AS3 or alternatively oligonucleotide probes that selectively bind to DNA encoding AS3.

The teachings of the specification cannot be extrapolated to the enablement of the use of the invention commensurate in scope with the claims because the specification does not provide sufficient guidance to enable one skilled in the art to use the invention with a reasonable expectation of success without first having to perform extensive and undue experimentation. In particular, it is noted that the specification does not exemplify the use of the invention to diagnose a mammal with any proliferative cell disorder or to assess the likelihood that the mammal will develop any such disorder. Furthermore, the specification does not exemplify the use of the invention to determine whether or not a subject is at increased risk for developing prostate cancer. Clearly, in the absence of the necessary guidance, one skilled in the art would not be able to use the invention with a reasonable expectation of success without performing undue experimentation. Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. Because of the high level of unpredictability in the art, one skilled in the art would not accept the assertion that the invention can be used to successfully in the absence of working exemplification.

With particular regard to the claimed method for diagnosing an individual with a proliferative cell disorder, clearly the specification provides insufficient guidance to enable the skilled artisan to practice the claimed invention with a

reasonable expectation of success. In particular, it is noted that the specification fails to disclose the threshold value of the difference in the levels of expression of the gene encoding AS3 in the different specimens that can be used to discriminate the individual that has primary or metastatic prostate cancer from the individual that is disease-free. Furthermore, based only upon the disclosure, one skilled in the art would not accept the assertion that the claimed method can be used successfully in the absence of working exemplification, because the art is highly unpredictable and therefore clinical applicability of the claimed method can only be determined empirically. There is no factual evidence of record that would reasonably convince one skilled in the art that the invention can be used to effectively diagnose any type of a proliferative cell disorder such as cancer, even though Applicants disclose that AS3 is either absent or expressed at a reduced level in some prostate cancer cells.

The molecular diagnosis of cancer is a highly unpredictable art. For example, Rae, et al (*International Journal of Cancer* **88**: 726-732, 2000) teach a method for determining the differential expression of genes in renal cell carcinoma (RCC) (abstract). Rae, et al disclose that a total of sixteen tumor and sixteen adjacent normal tissue samples were collected at the same time from patients. Rae, et al also disclose that the tumor tissue was histologically confirmed to be clear-cell RCC and the tumors were staged by a conventional system (page 726, column 2). Rae, et al teach that the use of differential display PCR, some genes were identified that are expressed at higher levels in the tumor specimens than in the normal specimens while other genes were expressed at lower levels in the tumor specimens (abstract). In any case, Rae, et al, disclose, "only those cDNAs cleary up- or down-regulated in duplicate paired RCC and normal kidney samples (Fig. 1) from 4 different patients were considered to be definitively differentially expressed" (page 728, column 1). Rae, et al teach that results were considered only when the cDNAs were successfully re-amplified and only when no expression was detected in the paired sample (page 728, column 2). Notably, Rae, et al had planned to use as a positive control primers that amplify a cDNA encoding DD96, a gene previously shown by Kocher, et al to be

up-regulated in RCC (page 728, column 2). However, Rae, et al found in contrast to the results reported by Kocher, et al, no *consistent* up- or down-regulation of *DD96* was evident when using either RT-PCR or Northern analysis. Rae, et al, therefore, conclude, "we do not believe that *DD96* up-regulation is highly associated with RCC, particularly in early progression, and does not warrant extensive further investigation in the context of this disease" (page 731, column 2). Certainly, at the very least, the teachings of Rae, et al suggest that it will be necessary to carefully and thoroughly investigate the claimed methods for diagnosis before attempting to practice such methods in a clinical setting, because otherwise one skilled in the art cannot know whether the invention can be used with a reasonable expectation of success.

Thus, in view of the teachings of Rae, et al, it is evident that the instant disclosure is not enabling, because in the absence of substantial factual evidence that the invention can be used to diagnose a proliferative cell disorder in a patient or any other mammalian subject, one of skill in the art cannot predict whether the invention can be used and would therefore not be able to practice the invention with a reasonable expectation of success without first performing extensive and undue experimentation.

In addition, it is unclear whether or what role AS3 has in the etiology or pathology of prostate cancer or any other proliferative cell disorder. It is entirely possible that the alteration in the level of expression of the nucleic acid molecule encoding AS3, which was observed in the prostate cancer cell line analyzed by Applicants, is the result of some epigenetic event(s) that occur late in tumor cell development. If so, there is little reason to expect the invention to be a valuable diagnostic marker, because one skilled in the art appreciates the fact that only early diagnosis is efficacious in treating the disease.

Ward (*Developmental Oncology* **21**: 91-106, 1985) teaches, not all markers can be reliably used in primary diagnosis; rather, some markers are more useful as guides in monitoring the efficacy of treatment modules for malignant disease (see abstract). Thus, while it is clear that a prostate cancer cell line may have an altered level of expression of the nucleic acid molecule

encoding AS3, this data does not guarantee that the detection of the relative level of over-expression or under-expression will result in a definitive diagnosis of the disease.

It is well known in the art that the detection of some tumor markers has proven to be ineffective in enabling an accurate diagnosis of cancer in a subject. Ward (cited supra) teaches that a number of tumor-associated markers are, in fact, diagnostically unreliable (see abstract). Even if the detection of an altered level of expression of the nucleic acid molecule encoding AS3 were found to clinically useful, there are insufficient guidelines for use of the resultant data acquired by the detection such a marker in the specification to enable one skilled in the art to use the invention to diagnose an individual with cancer. Tockman et al (*Cancer Research* **52**: 2711s-2718s, 1992) teach considerations necessary in bringing a cancer biomarker (intermediate endpoint marker) to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to risk assessment, diagnosis, and/or prognosis of any type of cancer. Tockman et al teach that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence, and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and **if validated** (emphasis added) can be used for population screening (page 2713, column 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and link those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate endpoint marker (page 2714, column 1). Clearly, prior to the successful application of newly described

markers, these must be validated against acknowledged disease end points; and, the marker predictive value must be confirmed in prospective population trials (page 2716, column 2).

With particular regard to the claimed method for assessing whether a subject is more likely to or has increased risk for developing a proliferative cell disorder or prostate cancer, *per se*, it is appropriately noted that the specification does not teach the value of the risk factor associated with a deficient or insufficient level of expression of the gene encoding AS3. In fact, the specification does not teach that a scientifically and clinically significant relationship exists between the measure of expression of AS3 and the occurrence or recurrence of prostate cancer or some other proliferative cell disorder in a subject. Clearly one skilled in the art cannot practice the claimed invention without having access to this correlative data, because without the data it is not possible to calculate a subject's risk for developing cancer. In addition, in view of the unpredictability in the art of at-risk assessment, one skilled in the art cannot predict the value of this risk factor without undue experimentation. For that matter, it is noted that the specification does not provide a disclosure that would enable one of skill in the art to accurately assess the value of this risk factor. Thus, the invention cannot be used to identify an individual at-risk for developing prostate cancer or any other proliferative cell disorder, including other types of cancer and certain autoimmune disorders, for example. If the claimed invention cannot be used to identify an individual at risk for developing prostate cancer or other proliferative cell disorder, it is obviously not possible to prevent the onset of the disease in individuals who are determined to be at-risk due to a deficiency or insufficiency in the level of AS3. Nevertheless, it is not currently possible to prevent the onset of prostate cancer in any subject, regardless of risk. For example, while certain genetic risk factors for developing familial breast cancer are well established (e.g., BRCA1 mutations), it is still not possible to prevent the occurrence of the disease, even in individuals who were known to be highly at-risk before the primary diagnosis was made. However, as stated in the 35 USC § 101 rejection above, the specification does not actually teach what

specific steps can be taken to prevent the onset of prostate cancer or any other proliferative cell disorder. The following supports these conclusions:

There is no evidence that measuring the level of expression of the gene encoding AS3 can result in an accurate estimate of a subject's risk for developing any particular proliferative cell disorder or prostate cancer, *per se*. This latter point is particularly relevant in view of the fact that cancer etiology is multi-factorial. Clearly, a measure of the level of AS3 in a cell cannot be a reliable predictor of a subject's risk for developing cancer, because there are so many other risk factors that must also be analyzed, and their contributions weighed. Also, apparently, the premise of the invention is that the gene encoding AS3 is either not expressed or expressed at reduced levels in the cancerous cells of the individual; however, on the basis of such a premise, one would not necessarily expect to find an absence or a reduction in the expression of the gene in a *normal* cell. Consequently, it is not apparent how measuring the level of expression of the gene encoding AS3 in an individual's normal cells will facilitate the determination of whether or not the individual is at greater risk for developing the disease. There are no examples that teach the actual identification of subjects at risk for developing a proliferative cell disorder such as prostate cancer. There is no correlative analysis that demonstrates that the proposed relationship between a subject's risk for developing a disease and the occurrence or recurrence of the disease in the subject is scientifically or clinically significant. Thus, the specification has not evidenced the usefulness of the invention to accurately assess risk or to use risk assessment to prevent the onset of a disease in a subject determined to be at risk for developing the disease.

At any rate, at this time, there is no immediately apparent benefit to determining the probability that an individual will develop cancer or some other proliferative cell disorder, because the onset of such diseases cannot be prevented and many so-called "prophylactic" therapies are considered to be unwarranted. Regardless of the type of cancer, surgical resection of a primary tumor, which is clearly the most conventional method of treating cancer today is often not curative simply because not *all* cancer cells will have been removed.

Moreover, there are never guarantees that a patient will not later develop cancer at different and independent sites, which are remote from the focus of another tumor that has been surgically excised. Currently, prevention of cancer is an intractable problem. For that matter, no one method of treatment, let alone prophylaxis has yet become an established modality, which in a clinical setting consistently yields success. Thus, establishing a patient to be at risk for developing cancer or even procuring knowledge that a patient has previously *had* cancer cannot currently be used to prevent the onset or recurrence of the disease.

In summary, upon consideration of the issue set forth above, it is clear that one skilled in the art would not accept the assertion that the invention can be used effectively to diagnose a proliferative cell disorder of any type in the absence of exemplification that is commensurate in scope with the claims. Again, the specification does not actually teach by example the use of the claimed method to render a diagnosis of such a disorder. The claimed methods for determining a subject's risk for developing cancer are based only upon scientific premise and clearly Applicant's inventive concept has not been reduced to practice, as evidenced by the lack of exemplification in the specification. The premise of the invention may or may not be proved following further experimentation. Moreover, the asserted utility of the invention is entirely unproven and therefore reasonably considered incredible. As stated above, one skilled in the art cannot predict whether the inventions can be used effectively. Accordingly, the application is viewed merely as an invitation to one skilled in the art to experiment with the objectives to establish the value of a diagnostic or risk factor associated with deficient or insufficient expression of the gene encoding AS3. Therefore, one skilled in the art cannot use the invention with a reasonable expectation of success without first performing extensive and undue experimentation.

16. Claims 2, 4-12, 47, and 51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the

specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 2 and 4-12 encompass isolated genomic DNA molecules, messenger RNA (mRNA) molecules, and cDNA molecules, which encode allelic variants of the protein encoded by the polynucleotide sequence of SEQ ID NO: 1 or 3, provided that the allelic variants encode proteins comprising an amino acid sequence that is at least about 45% homologous to SEQ ID NO: 2 or else the polynucleotide sequences of the molecules comprise sequences that are at least 50% homologous to SEQ ID NO: 1 or 3. The claims encompass isolated differentially spliced mRNA molecules and cDNA molecules produced therefrom, which encode splice variants of the protein encoded the polynucleotide sequence of SEQ ID NO: 1 or 3, provided that the splice variants encode proteins comprising an amino acid sequence that is at least about 45% homologous to SEQ ID NO: 2 or else the polynucleotide sequences of the molecules comprise sequences that are at least 50% homologous to SEQ ID NO: 1 or 3. The claims also encompass isolated genomic DNA molecules comprising polynucleotide sequences that encode allelic variants, provided that the polynucleotide sequences comprise sequences that are at least 50% homologous to SEQ ID NO: 1 or 3 or encode polypeptides that comprise an amino acid sequence that is at least about 45% homologous to SEQ ID NO: 2.

The specification only discloses the sequence of a mammalian cDNA molecule, which is set forth as SEQ ID NO: 1, and the open reading frame thereof, which is set forth as SEQ ID NO: 3. Further, the specification discloses that the cDNA molecule encodes a protein that has the polypeptide sequence set forth as SEQ ID NO: 2. However, as stated in the paragraph above, the claims encompass a broad genus of nucleic acid molecules. The structures and polynucleotide sequences of the vast majority of these congeneric species of nucleic acid molecules are not disclosed in the specification. The disclosure of a single species of the claimed genus of nucleic acid molecules, namely SEQ ID

NO: 1 is considered insufficient to meet the written description requirement of 35 USC § 112, first paragraph.

The specification does not disclose any one member of the claimed species of nucleic acid molecules that encode at least a portion of a protein having an amino acid sequence that homologous to SEQ ID NO: 2. Also, the disclosure fails to adequately describe a representative number of the members of claimed genus of nucleic acid molecules.

Consequently, there appears to no factual evidence in the specification that would serve to reasonably convey to one skilled in the art that Applicants had possession of the claimed invention at the time the application was filed. *Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (page 1116).

In addition, Applicants are reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (page 1115). Applicants are further reminded that conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation.

Certainly, in view of the high level of unpredictability in the art, as was noted above, the disclosure that the members of the claimed genus of nucleic acid molecules have homology to SEQ ID NO: 1 or 3 or encode a protein or portion thereof that has a polypeptide sequence that is homologous to SEQ ID NO: 2 is not sufficient to enable one skilled in the art to immediately visualize or recognize the identity of the members of the genus.

The Federal Circuit recently clarified the application of the written description requirement to inventions in the field of biotechnology. See *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1568, 43, USPQ2d 1398, 1406 (Fed. Cir. 1997). The Court stated, "[a] written description of an

invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name', of the claimed subject matter sufficient to distinguish it form other materials" (Id. at 1567, 43 USPQ2d at 1405). The Court also stated, "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material" (Id.). Furthermore, the Court indicates that an adequate description of a genus may be achieved by means of a recitation of a representative number of members of the genus or a recitation of specific structural features common to members of the genus, which constitute a substantial portion of the genus. With regard to the instant application, the specification fails to identify a representative number of members of the genus, but moreover, the specification does not include a description of a structural feature, such as a region of sequence that is essential to the function of the protein encoded by the cDNA molecules, which is common to the members of the genus.

Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method for isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

With the exception of SEQ ID NO: 1, the skilled artisan cannot immediately envision the detailed structure of the claimed polynucleotides. Consider, for example, that the gene encoding human AS3 would be expected to have both introns and exons as well as regulatory elements. While it is not clear if the specification identifies and describes the entirety of the 5'- and 3'- regulatory regions, including the promoter, and untranslated regions of the human gene, which are essential to the function of the claimed invention, it is clear that the specification fails to adequately describe the introns of the gene since the sequences of the introns are not disclosed. The art also indicates that the structures of the introns of genes must be empirically determined. See Cawthon et al, *Genomics* 9: 446-460, 1991). Obviously, in view of the teachings

of Cawthon, et al, the structure of introns is not conventional. The structure of a gene is not defined only by disclosure of the coding sequences and the boundaries of the introns and exons, because it is still not possible to work backward from knowledge of the structure of a cDNA molecule to derive the structure of the gene encoding the mRNA from which the cDNA was produced. Therefore, in the absence of adequate disclosure describing the introns of the gene, one skilled in the art would not be reasonably convinced that Applicant was in possession of the claimed genus of nucleic acid molecules, which including any and all genes that encode the polypeptide of SEQ ID NO: 2 or any homologue thereof. Consequently, the disclosure is insufficient to meet the written description requirement of 35 USC 112, first paragraph and to support the generic claims in accordance with *The Guidelines for Examination of Patent Applications* (66 FR 1099-1111, 5 January 2001).

With particular regard to claims 47 and 51, the claims are drawn to a genus of methods for diagnosing a proliferative cell disorder and/or methods for assessing an individual's risk for developing a proliferative cell disorder or prostate cancer, *per se*; however, in view of the issues above, it is clear that the written description is insufficient to reasonably convey to one skilled in the art that Applicants' had possession of the invention at the time the application was filed. Evidence of conception of an invention alone is not reasonable inference that Applicants' had possession of the invention at the time the application was filed. In the absence of exemplification and sufficient guidance, there is no factual evidence of record that would suggest that a reduction to practice had occurred at the time the application was filed. For this reason, the specification fails to meet the written description requirement of 35 USC § 112, first paragraph.

17. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

18. Claims 4-12, 47-49, and 51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4 and 6-12 are indefinite because claim 4 recites "[a]n isolated nucleic acid molecule which encodes a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 2. This recitation renders the claim indefinite because it is unclear to what subject matter the claim refers. For example, it is unclear that there is a nucleic acid molecule that encodes a naturally occurring allelic variant of a polypeptide, wherein said polypeptide comprises SEQ ID NO: 2. Perhaps, instead, Applicants regard as the invention an isolated nucleic acid molecule encoding a naturally occurring allelic variant of the polypeptide of SEQ ID NO: 2 or in other words, an isolated allelic sequence comprising a polynucleotide sequence that differs from the polynucleotide sequence of the nucleic acid molecule encoding SEQ ID NO: 2 by the one or more polymorphisms. In view of the uncertainty of the claimed subject matter, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claims 5 and 6-12 are indefinite because claim 5 recites the limitation "a nucleic acid molecule which encodes a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO:2, wherein the fragment comprises at least 15 contiguous amino acid residues of the amino acid sequence of SEQ ID NO:2". This recitation renders the claim indefinite because it is unclear to what subject matter the claim refers. For example, it is unclear whether the claim is drawn to an isolated nucleic acid molecule that encodes a protein comprising at least 15 contiguous amino acids of SEQ ID NO: 2 or an isolated nucleic acid molecule that encodes a fragment, which comprises at least 15 contiguous amino acid residues of SEQ ID NO: 2, of a protein comprising SEQ ID NO: 2. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claim 6 is vague and indefinite because the claim recites the phrase "under stringent conditions". Stringent conditions are not defined by the claim

and therefore the claim encompasses fully ranging stringent conditions, i.e., ranging from conditions of low to high permissiveness). Because the specification does not provide a standard for ascertaining the requisite degree of stringency, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention. Amending the claim to recite the specific hybridization conditions that the claim requires can obviate this rejection.

Claims 47-49 and 51 are indefinite because the claims recite the lab designation "AS3" as the sole means of identifying the nucleic acid molecule or polypeptide to which the claims refer. The use of laboratory designations only to identify a particular nucleic acid molecule or polypeptide renders a claim indefinite because different laboratories may use the same laboratory designations to define completely distinct nucleic acid molecules or polypeptides. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention. Amendment of the claims to include the amino acid sequence of the polypeptide or the polynucleotide sequence of the nucleic acid molecule by reference to a specific sequence identification number can obviate this rejection, because the amino acid sequence of a polypeptide and the polynucleotide sequence of a nucleic acid molecule are unique identifiers that unambiguously define a given polypeptide or nucleic acid molecule.

Claim 47 is vague and indefinite because the claim recites the phrase "a disease involving altered cell proliferation". Recitation of the phrase renders the claim vague and indefinite because it cannot be ascertained to which disease(s) and to which cell(s) the claim refers. Moreover, it is unclear how or to what extent the claim requires the proliferation of the cell(s) to be altered and the specification does not provide a standard for ascertaining the requisite degree of alteration. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claim 47 is also vague and indefinite because the claim recites the phrase "an increased likelihood". The term "increased" is a relative term, but it is not clear from the claim to what the likelihood that a mammal will develop a disease is to be compared. Moreover, use of the relative term renders the claim vague

and indefinite because it cannot be ascertained to what degree of increase the claim requires the likelihood to be increased in order that the mammal be considered as having an increased likelihood of developing the disease and the specification does not provide a standard for determining the requisite degree of increase. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claim 48 is indefinite because the claim does not recite a positive process step that clearly relates back to the preamble of the claim. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention. Amending the claim to recite, for example, the phrase "whereby a AS3 polypeptide is obtained" at the end of the last line of the claim can obviate this rejection.

Claim 49 is indefinite because the claim does not recite a positive process step that clearly relates back to the preamble of the claim. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention. Amending the claim to recite, for example, the phrase "whereby a AS3 gene or portion thereof is isolated" at the end of the last line of the claim can obviate this rejection.

Claim 51 is vague and indefinite because the claim recites the phrase "at increased risk". The term "increased" is a relative term, but it is not clear from the claim to what the risk that a subject will develop prostate cancer is to be compared. Moreover, use of the relative term renders the claim vague and indefinite because it cannot be ascertained to what degree of increase the claim requires the risk to be increased in order that the subject be considered as being at increased risk for developing prostate cancer and the specification does not provide a standard for determining the requisite degree of increase. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claim 51 is also vague and indefinite because the claim recites the tern "reduced". The term "reduced" is a relative term, but it is not clear from the claim to what the level of AS3 is to be compared in order to determine whether or not a

reduction in the level is evident. Moreover, use of the relative term renders the claim vague and indefinite because it cannot be ascertained to what degree of reduction the claim requires the level of expression of AS3 to be reduced in order that the subject be considered as being at increased risk for developing prostate cancer and the specification does not provide a standard for determining the requisite degree of the reduction. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claim 51 is also vague and indefinite because the claim recites the phrase "probes that selectively bind to DNA encoding AS3". Because it is highly probable that the DNA encoding AS3 can be found in every cell of every subject, regardless of whether or not the subject is at relatively increased risk for developing prostate cancer, it is unclear how detecting the presence of AS3 of the DNA will lead to a determination that a subject is at increased risk for developing prostate cancer. Therefore, the Examiner questions if the claim particularly point outs and distinctly claims the subject matter that Applicants actually regard as the invention. Also, it is noted that the format of claim 51 appears to be inappropriate since the kit only comprises (a) and (b) and not (c) and (d).

Claim Rejections - 35 USC § 102

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

20. Claims 5-12, 47-49, and 51 are rejected under 35 U.S.C. 102(a) as being anticipated by Geck, et al (*Journal of Steroid Biochemistry and Molecular Biology* **6**: 41-50, 1999; Form PTO-1449, citation A3).

With regard to claims 47 and 51, the claims are drawn to a kit comprising a material for measuring AS3 RNA and at least one reagent that specifically detects an AS3 molecule, respectively, wherein said reagent is an oligonucleotide probe that selectively binds to DNA encoding AS3. Claim 47 recites that the kit is to be used to diagnose a mammal with a disorder or to assess the likelihood that the mammal will develop the disorder. Claim 51 recites the kit is to be used to determine if a subject is at increased risk for developing prostate cancer. In the instance of both claims 47 and 51, however, those limitations are viewed as recitations of intended use and therefore are not given weight in comparing the claim with the prior art. Accordingly, claims 47 and 51 read on the ingredients *per se*, which are the material and the oligonucleotide that selectively binds DNA encoding AS3. In addition, it is noted that claim 51 recites the kit contains instructions for its use. However, the copy of instructions for use is non-statutory subject matter and cannot be relied upon to provide patentability, because the instructions impart no new or limiting feature to the oligonucleotide. Consequently, as stated previously, claim 51 reads only on an oligonucleotide that selectively binds to DNA encoding AS3.

Geck, et al teach the polynucleotide sequence of an isolated nucleic acid molecule that encodes human AS3 (pages 43 and 44, Figure 1), which comprises a nucleotide sequence that is at least 50% homologous to the sequence of SEQ ID NO: 1 and the complement thereof. Furthermore, Geck, et al disclose the amino acid sequence of human AS3 in Figure 1, which includes an amino acid sequence that is at least about 45% homologous to the sequence of SEQ ID NO: 2. Also, Geck, et al disclose an expression vector and a method involving culturing host cell that comprise the expression vector, wherein the expression vector comprises at least a portion of the polynucleotide sequence that encodes AS3 (page 42, columns 1 and 2; page 45, columns 1 and 2). Geck, et al disclose a method and a material for measuring mRNA encoding AS3 (page

42, columns 1 and 2). Geck, et al teach a method for isolating a genomic DNA molecule encoding at least a portion of AS3, wherein the polynucleotide sequence has identity to the sequence encoding human AS3 (page 47, column 1, Figure 4; page 48, column 2, Figure 5). Geck, et al teach oligonucleotides that selectively bind to the DNA encoding AS3 (page 45, columns 1 and 2).

All the limitations of the claims are met.

21. Claims 5-7, 9-11, 47, and 51 are rejected under 35 U.S.C. 102(b) as being anticipated by Geck, et al (Journal of Steroid Biochemistry and Molecular Biology 63: 211-218, 1997; Form PTO-1449, citation A2).

Geck, et al teach an isolated nucleic acid molecule that encodes at least a portion of human AS3 (abstract; page 214, Table 1). Also, Geck, et al disclose an expression vector and a method involving culturing host cell that comprise the expression vector, wherein the expression vector comprises at least a portion of the polynucleotide sequence that encodes AS3 (page 212, columns 1 and 2). Geck, et al disclose a method and a material for measuring mRNA encoding AS3 (page 213, column 1). Geck, et al teach oligonucleotides that selectively bind to the DNA encoding AS3 (page 214, Figure 4).

All the limitations of the claims are met.

Note: Geck, et al do not explicitly disclose the polynucleotide sequence of the isolated nucleic acid molecule. Nevertheless, the prior art nucleic acid molecule is deemed the same as the nucleic acid molecule of the instant claims, because the polynucleotide sequence is an inherent property of a nucleic acid molecule.

22. Claims 5-7, 47, and 51 are rejected under 35 U.S.C. 102(b) as being anticipated by GenBank Accession No. U95825 (Geck, et al, Direct Submission, 28 March 1997).

The polynucleotide sequence of the isolated nucleic acid molecule of GenBank Accession No. U95825 comprises a nucleotide sequence that is at least 50% homologous to the sequence of SEQ ID NO: 1 and the complement

thereof and encodes human AS3. The amino acid sequence of human AS3, which would be encoded by the nucleic acid molecule, includes an amino acid sequence that is at least about 45% homologous to the sequence of SEQ ID NO: 2.

All the limitations of the claims are met.

23. Claims 5-7, 9, 47, and 51 are rejected under 35 U.S.C. 102(b) as being anticipated by GenBank Accession No. U50533 (Simard, Direct Submission, 04 March 1996).

The polynucleotide sequence of the isolated nucleic acid molecule of GenBank Accession No. U50533 comprises a nucleotide sequence, which comprises a fragment of at least 250 nucleotides of a nucleic acid comprising the sequence of SEQ ID NO: 1 and which encodes a polypeptide comprising an amino acid sequence that is at least about 45% homologous to the amino acid sequence of SEQ ID NO: 2, and further comprises a nucleotide sequence encoding a heterologous polypeptide. The annotation indicates in which vector the nucleic acid molecule is cloned.

All the limitations of the claims are met.

24. Claims 4-9 and 47 are rejected under 35 U.S.C. 102(a) as being anticipated by GenBank Accession No. AB023196 (Ohara, et al, Direct Submission, 04 February 1999).

The polynucleotide sequence of the isolated nucleic acid molecule of GenBank Accession No. AB023196 comprises a nucleotide sequence, which comprises a fragment of at least 250 nucleotides of a nucleic acid comprising the sequence of SEQ ID NO: 1 and which encodes a polypeptide comprising an amino acid sequence that is at least about 45% homologous to the amino acid sequence of SEQ ID NO: 2, and further comprises a nucleotide sequence encoding a heterologous polypeptide. The annotation indicates in which vector the nucleic acid molecule is cloned.

All the limitations of the claims are met.

25. Claims 5-9 are rejected under 35 U.S.C. 102(b) as being anticipated by GenBank Accession No. BF509252 (National Cancer Institute - Cancer Genome Anatomy Project, Unpublished, 1997).

The polynucleotide sequence of the isolated nucleic acid molecule of GenBank Accession No. BF509252 comprises a nucleotide sequence, which encodes a polypeptide comprising an amino acid sequence that is at least about 45% homologous to the amino acid sequence of SEQ ID NO: 2, and a nucleotide sequence encoding a heterologous polypeptide. The annotation indicates in which vector the nucleic acid molecule is cloned.

All the limitations of the claims are met.

Claim Rejections - 35 USC § 103

26. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

27. Claims 1, 2, 5-12, 47-49, and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Geck, et al (*Journal of Steroid Biochemistry and Molecular Biology* **6**: 41-50, 1999; Form PTO-1449, citation A3).

Geck, et al teach that which is stated in the corresponding 35 USC §102(a) rejection above.

It is noted that the polynucleotide sequence of the isolated nucleic acid molecule of Geck, et al and the polypeptide sequence of AS3, which Geck, et al disclose, differ from the polynucleotide sequence of SEQ ID NO: 1 and 3 and SEQ ID NO: 2, respectively. Nonetheless, the prior art nucleic acid molecule and the protein that is encoded by said nucleic acid molecule are deemed the same as the nucleic acid molecule and protein encoded by said nucleic acid of the instant claims, absent a showing of any unobvious differences.

However, Geck, et al do not explicitly disclose a method for obtaining AS3 that involves culturing a cell that expresses a nucleic acid molecule encoding AS3 and then isolating AS3.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use an expression vector comprising the isolated cDNA molecule of Geck, et al, which encodes AS3, to obtain AS3 by a process of culturing host cells transfected with the expression vector under conditions that are appropriate for expression of the cDNA molecule to produce the protein and isolating the protein so produced, because such methodology was conventional and routine. One of ordinary skill in the art at the time the invention was made would have been motivated to obtain AS3 for use in producing an reagent antibody that binds specifically to AS3 for additional studies designed to further elucidate the biologic function of AS3.

28. Claims 5-12, 47-49, and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Geck, et al (*Journal of Steroid Biochemistry and Molecular Biology* **63**: 211-218, 1997; Form PTO-1449, citation A2).

Geck, et al teach that which is stated in the corresponding 35 USC §102(a) rejection above.

However, Geck, et al do not explicitly disclose a method for obtaining AS3 that involves culturing a cell that expresses a nucleic acid molecule encoding AS3 and then isolating AS3. Also, Geck, et al do not explicitly disclose that the nucleic acid molecule encoding AS3 comprises a nucleotide sequence encoding a heterologous polypeptide.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use an expression vector comprising the isolated cDNA molecule of Geck, et al, which encodes AS3, and a nucleic acid comprising a heterologous polypeptide, namely the FLAG epitope to obtain a fusion protein comprising AS3 and the FLAG epitope by a process of culturing host cells transfected with the expression vector under conditions that are appropriate for expression of the nucleic acid molecule to produce the fusion

protein and isolating the fusion protein so produced, because such methodology was conventional and routine. One of ordinary skill in the art at the time the invention was made would have been motivated to make the expression vector encoding the fusion protein comprising AS3 and the FLAG epitope, because antibodies that bind specifically to the FLAG epitope were commercially available and could be used to immunoprecipitate the fusion protein to facilitate its isolation and purification. One of ordinary skill in the art at the time the invention was made would have been motivated to thus obtain the fusion protein comprising AS3 and the FLAG epitope for use in producing an reagent antibody that binds specifically to AS3 for additional studies designed to further elucidate the biologic function of AS3.

29. Claims 1, 2, 5-7, 47, and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over GenBank Accession No. U95825 (Geck, et al, Direct Submission, 28 March 1997).

As stated in the corresponding 35 USC §102(b) rejection above, the polynucleotide sequence of the isolated nucleic acid molecule of GenBank Accession No. U95825 comprises a nucleotide sequence that is at least 50% homologous to the sequence of SEQ ID NO: 1 and the complement thereof and encodes human AS3. The amino acid sequence of human AS3, which would be encoded by the nucleic acid molecule, includes an amino acid sequence that is at least about 45% homologous to the sequence of SEQ ID NO: 2.

It is noted that the polynucleotide sequence of the isolated nucleic acid molecule of GenBank Accession No. U95825 differs from the polynucleotide sequence of SEQ ID NO: 1. Nevertheless, the prior art nucleic acid molecule is deemed the same as the nucleic acid molecule of the instant claims, absent a showing of any unobvious differences. The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics of the claimed product or the protein encoded thereby would not function identically as the claimed nucleic

acid and the protein encoded thereby. In the absence of evidence to the contrary, the burden is upon the Applicants to prove that the claimed nucleic acid molecule and the protein encoded thereby are functionally different than those taught by the prior art and to establish patentable differences. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Board of Patent Appeals and Interferences).

Conclusion

30. No claims are allowed.

31. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Thursday, alternate Fridays, 8:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

DONNA WORTMAN
PRIMARY EXAMINER

slr
November 16, 2001

Notice to Comply	Application No.	Applicant(s)	
	09/512,581	SOTO ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other:

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

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